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Nickel-Catalyzed [2 + 2 + 2] Cycloaddition of Two Enones and an Alkyne

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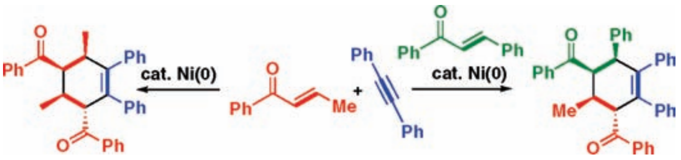
ABSTRACT



A fully intermolecular [2 + 2 + 2] cycloaddition of two enones and an alkyne has been achieved. This reaction proceeds stereoselectively to give one diastereomer as a sole product.

Transition-metal-catalyzed [2 + 2 + 2] cycloaddition is one of the most powerful methods used to accomplish the one-step construction of a variety of six-membered ring compounds. Nickel(0) complexes have been employed as efficient catalysts for [2 + 2 + 2] cycloaddition reactions of two alkynes with other unsaturated compounds, such as an enone, an α,*β*-unsaturated ester, carbon dioxide, an isocyanate, a nitrile, and an imine.[1] On the other hand, Montgomery reported the nickel-catalyzed [2 + 2 + 2] cycloaddition of an alkynyl-enone with an enone (eq 1).[2] This reaction is noteworthy, since transition-metal-catalyzed [2 + 2 + 2] cycloaddition of two alkenes and an alkyne is still limited to only a few examples,[3] and no fully intermolecular reaction has yet been reported.[4] In the nickel-catalyzed reaction of enones with alkenes,[5] the formation of a three-component addition product of two enones and an ethylene has been reported (eq 2).[5a]

Here, we report a fully intermolecular [2 + 2 + 2] cycloaddition reaction of two enones and an alkyne. The

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(1) Enone: (a) Ikeda, S.; Mori, N.; Sato, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4779. (b) Mori, N.; Ikeda, S.; Sato, Y. *J. Am. Chem. Soc.* **1999**, *121*, 2722. (c) Sambaiah, T.; Li, L.; Huang, D.; Lin, Cheng; Rayabarapu, D. K.; Cheng, C. *J. Org. Chem.* **1999**, *64*, 3663. (d) Qui, Z.; Xie, Z. *Angew. Chem., Int. Ed.* **2009**, *48*, 5729. Isocyanate: (e) Duong, H. A.; Cross, M. J.; Louie, J. *J. Am. Chem. Soc.* **2004**, *126*, 11438. (f) Duong, H. A.; Louie, J. *J. Organomet. Chem.* **2006**, *62*, 7552. CO_2: (g) Inoue, Y.; Itoh, Y.; Hashimoto, H. *Chem. Lett.* **1978**, 633. (h) Tsuda, T.; Morikawa, S.; Hasegawa, N.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 2978. (i) Louie, J.; Gibby, J. E.; Farnworth, M. V.; Takavec, T. N. *J. Am. Chem. Soc.* **2002**, *124*, 15188. Nitrile: (j) McCormick, M. M.; Duong, H. A.; Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2005**, *127*, 5030. Aldehyde: (k) Tsuda, T.; Kiyoi, T.; Miyane, T.; Saegusa, T. *J. Am. Chem. Soc.* **1988**, *110*, 8570. (l) Takavec, T. N.; Louie, J. *Org. Lett.* **2005**, *7*, 4037. Imine: (m) Ogoshi, S.; Ikeda, H.; Kurosawa, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 4930. Review: (n) Chopadea, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307, and references cited therein.

(2) Seo, J.; Chui, H. M. P.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 476.

(3) Alkene-alkene-alkyne: (a) Trost, B. M.; Imi, K.; Indolese, A. F. *J. Am. Chem. Soc.* **1993**, *115*, 8831. (b) Lautens, M.; Tam, W.; Lautens, J. C.; Edwards, L. G.; Crudden, C. M.; Smith, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 6863. (c) Shibata, T.; Tahara, Y.-k. *J. Am. Chem. Soc.* **2006**, *128*, 11766. (d) Tanaka, K.; Nishida, G.; Sagae, H.; Hirano, M. *Synlett* **2007**, 1426. (e) Tanaka, D.; Sato, Y.; Mori, M. *J. Am. Chem. Soc.* **2007**, *129*, 7730.

(4) Reppe suggested the formation of [2 + 2 + 2] cycloaddition product of acetylene, butyl acrylate, and butyl vinyl ether in 16% yield only by elemental analysis and boiling point: Reppe, W.; Schweckendiek, W. J. *Justus Liebigs Ann. Chem.* **1948**, *560*, 104.

(5) (a) Ogoshi, S.; Nishimura, A.; Haba, T.; Ohashi, M. *Chem. Lett.* **2009**, *38*, 1166. (b) Ogoshi, S.; Haba, T.; Ohashi, M. *J. Am. Chem. Soc.* **2009**, *131*, 10350.

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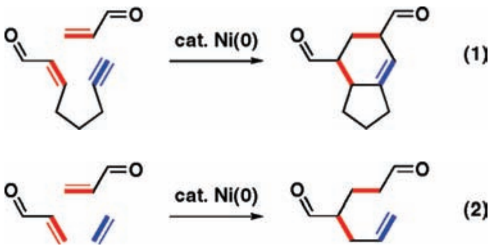
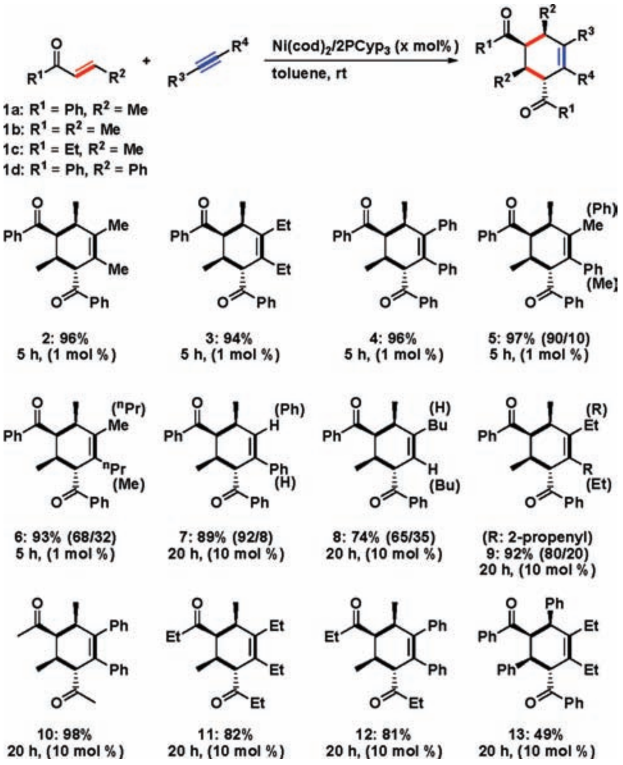


isolation of a key intermediate complex and its reaction with the second enone is also discussed.

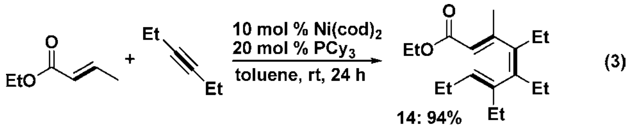
In the presence of Ni(cod)$_2$ and PCyp$_3$, the reaction of (*E*)-1-phenyl-2-buten-1-one (**1a**) with 2-butyne (1 equiv) occurred to give a [2 + 2 + 2] cycloaddition product **2** as a sole product in 96% isolated yield (Scheme 1). The molecular structure of **2** was determined by X-ray crystallography.

Scheme 1. [2 + 2 + 2] Cycloaddition of Two Enones with an Alkyne[a,b]



[a] Isolated yield. [b] Substituent of minor regioisomer in parentheses.

The reaction of **1a** with 3-hexyne and diphenylacetylene also proceeded under the same reaction conditions to give **3** (94%) and **4** (96%), respectively. The reaction with phenylpropyne, 2-hexyne, phenyl acetylene, 1-hexyne, and 2-methyl-1-hexen-3-yne also proceeded to give **5** (97%), **6** (93%), **7** (89%), **8** (74%), and **9** (92%), respectively, as a mixture of regioisomers. The regioselectivity of the reaction with phenylpropyne, pheylacetylene, and 2-methyl-1-hexen-3-yne is much better than that of the reaction with 2-hexyne and 1-hexyne, which might be due to the contribution of either an η^3-benzyl or an η^3-allyl structure in a possible intermediate.[6,7] Both (*E*)-3-penten-2-one (**1b**) and (*E*)-4-hexene-3-one (**1c**) reacted with alkynes to afford **10**, **11**, and **12** in high yield. Chalcone (**1d**) also reacted with 3-hexyne to give the expected cyclohexene **13** (49%) and a mixture of cyclohexadiene derivatives (7%) by cycloaddition of an enone and two alkynes.[1a,b] The reaction of ethyl (*E*)-2-butenoate with 3-hexyne (2 equiv) gave an acyclic hexatriene compound (**14**) in 94% isolated yield (eq 3),[8] rather than the expected cyclohexene compound. The corresponding aldehyde, (*E*)-2-butenal, did not react with 3-hexyne under the same reaction conditions.



To observe a possible reaction intermediate, the stoichiometric reaction of **1d** and diphenylacetylene with Ni(cod)$_2$ and PCyp$_3$ was conducted, and the expected nickelacycle complex (**15**) was isolated in 95% yield. The η^3-oxaallyl structure of **15** was revealed by X-ray crystallography, as shown in Figure 1.[9] The ^{1}H and ^{13}C NMR spectra in C$_6$D$_6$ were also consistent with an η^3-oxaallyl structure. The nickel complex **15** reacted with **1a** at room temperature in 30 min to give a [2 + 2 + 2] cycloaddition product (**16**) of **1d**, diphenylacetylene, and **1a** quantitatively (eq 4). On the other hand, the reaction of **15** with **1c** proceeded very slowly to give a mixture of the expected compounds **17** (50%) and **12** (37%). The formation of **12** suggests that the oxidative cyclization is a reversible process. Furthermore, treatment of **15** with a mixture of **1a** and **1c** gave **16** as a sole product, which suggests that **15** reacts with **1a** much faster than with **1c**. These observations suggested the possibility of the nickel-catalyzed [2 + 2 + 2] cycloaddition of two different enones with an alkyne. In the presence of Ni(cod)$_2$ and PCyp$_3$, the reaction of **1a** and **1d** with dipheny-

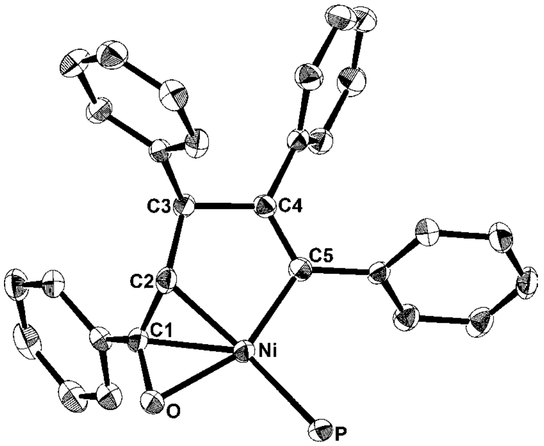
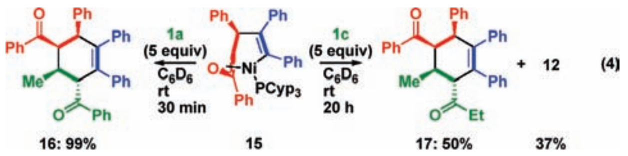
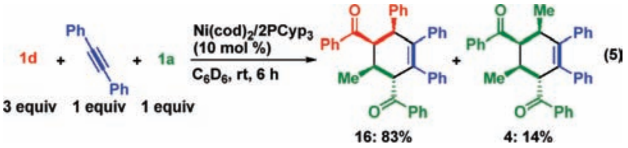


Figure 1. Molecular structure of **15** with thermal ellipsoids at the 30% probability level. Cyclopentyl groups and H atoms are omitted for clarity.

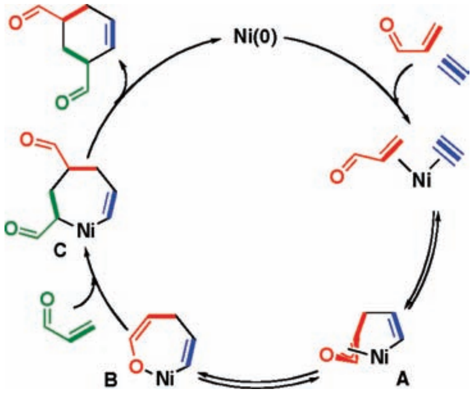
lacetylene gave the expected compounds **16** (83%) and **4** (14%) (eq 5). To date, a selective fully intermolecular [2 + 2 + 2] cycloaddition of three different components is very rare.[1d,4,10]





The reaction might proceed as follows. The oxidative cyclization of an enone and an alkyne with nickel(0) occurs to give an η^3-oxaallylnickel intermediate **A** which might be in equilibrium with its isomer, η^1-*O*-nickelenolate intermediate **B** (Scheme 2). Montgomery reported the isolation of a seven-membered η^1-*O*-nickelenolate by the oxidative cyclization of an alkenyl-enone with an Ni(0) complex.[9] The intermediate **B** reacts with the second enone to generate a seven-membered nickelacycle intermediate **C**. The inversion of the stereochemistry of the chalcone moiety in both **16** and **17** is consistent with the reaction mechanism via η^1-*O*-nickelenolate. The reaction of the six-membered η^1-*O*-nickelenolate with an enone to give a corresponding nickelacycle has been reported.[11] The reductive elimination from **C** gives a [2 + 2 + 2] cycloaddition product.

Scheme 2. Plausible Reaction Mechanism



In conclusion, we demonstrated the fully intermolecular [2 + 2 + 2] cycloaddition of two enones and an alkyne catalyzed by nickel(0) complexes. A reaction intermediate complex formed by the oxidative cyclization of an enone and an alkyne with Ni(cod)$_2$ and PCyp$_3$ was isolated, and its molecular structure was determined by X-ray crystallography. The reaction of the isolated nickel complex with an enone gave the corresponding [2 + 2 + 2] cycloaddition product. Moreover, this observation was expanded to include the nickel-catalyzed [2 + 2 + 2] cycloaddition of chalcone, diphenylacetylene, and (*E*)-1-phenyl-2-buten-1-one.

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Supporting Information Available: Detailed experimental procedures and analytical and spectral data for all new compounds and crystallographic data for **2**, **10**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) The contribution of the η^3-allyl structure on the regioselectivity in oxidative cyclization of 1,3-eneyne and aldehyde with nickel(0) has been reported: Liu, P.; McCarren, P.; Cheong, P. H.; Jamison, T. F.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 2050.

(7) A similar regioselectivity was observed in the reaction of enones and alkynes with aldehyde catalyzed by Ni(cod)$_2$ and PCy$_3$: (a) Herath, A.; Li, W.; Montgomery, J. *J. Am. Chem. Soc.* **2008**, *130*, 469. (b) Herath, A.; Li, W.; Montgomery, J. *J. Am. Chem. Soc.* **2009**, *131*, 7024.

(8) The molecular structure of **14** is inferred from the analogues reported in ref 1c

(9) The oxidative cyclization of alkynylenone with nickel(0) to give a cyclic *O*-nickel enolate has been reported by Montgomery and Schlegel: (a) Amarasinghe, K. K. D.; Chowdhury, S. K.; Heeg, M. J.; Montgomery, J. *Organometallics* **2001**, *20*, 370. (b) Hratchian, H. P.; Chowdhury, S. K.; Gutiérrez-García, V. M.; Amarasinghe, K. K. D.; Heeg, M. J.; Schlegel, H. B.; Montgomery, J. *Organometallics* **2004**, *23*, 4636.

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(11) (a) Ogoshi, S.; Nagata, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2006**, *128*, 5350. (b) Tamaki, T.; Nagata, M.; Ohashi, M.; Ogoshi, S. *Chem.−Eur. J.* **2009**, *15*, 10083.